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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/583,860	05/21/2007	Takashi Nishimura	3691-0133PUS1	8593

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EXAMINER	
CHEN, SHIN LIN	

ART UNIT	PAPER NUMBER
1632	

NOTIFICATION DATE	DELIVERY MODE
01/13/2011	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/583,860	NISHIMURA ET AL.	
	Examiner	Art Unit	
	Shin-Lin Chen	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 November 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-9 and 11-22* is/are pending in the application.

4a) Of the above claim(s) *6,14 and 18-21* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-5,7-9,11-13,15-17 and 22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendment filed 11-15-10 has been entered. Claims 1, 6-9 and 14-21 have been amended. Claims 1, 3-9 and 11-22 are pending. Claims 1, 3-5, 7-9, 11-13, 15-17 and 22 are under consideration.

Applicant requests rejoinder of claims 6, 14 and 18-21 to the examined claims because of the amendment to the claims (amendment, p. 7). This is not found persuasive because of the reasons set forth in the preceding Official action mailed 5-13-08 and the reasons discussed below that no common special technical feature is contributed by the instant invention over the prior art. The request for rejoinder is denied.

Claim Rejections - 35 USC § 103

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

2. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

3. Claims 1, 3, 4, 7-9, 11, 12, 15-17 and 22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kessels et al., 2001 (Nature Immunology, Vol. 2, No. 10, p. 957-961) in view of Fujio et al., 2000 (Journal of Immunology, Vol. 165, p. 528-532), Tsuji et al., April 2003 (Cancer Science, Vol. 94, No. 4, p. 389-393), and Nishimura, T., 2000 (Cancer Treatment and Host, Vol. 12, No. 4, p. 363-373, IDS-CL). Applicant's amendment filed 11-15-10 necessitates this new ground of rejection.

Claims 1, 3, 4, 7, 8 and 22 are directed to a process of preparing cells for cell therapy comprising inducing helper T1 cells that have a nonspecific antitumor activity from leukocytes isolated from a patient, and imparting antigen specificity to the helper T1 cells by transducing the helper T1 cells with a T cell receptor gene that recognizes a cancer-associated antigen, wherein the TCR gene is a MHC class I-restricted or class II-restricted T cell receptor gene. Claims 7 and 8 specify further purifying the Th1 cells to which antigen specificity has been imparted by using antibody-bearing magnetic beads. Claim 22 specifies the T1 cell receptor gene is isolated from a tumor specific human cytotoxic T cell clone. Claim 9, 11, 12 and 15-17 are directed to a process of preparing cells for cell therapy comprising inducing Th1 cells and Tc1 cells having a nonspecific antitumor activity and imparting antigen specifically to the Th1 cells and Tc1 cells by transducing the Th1 cells and Tc1 cells with a TCR gene that recognizes a cancer-associated antigen. Claims 11 and 12 specify transducing with MHC class I-restricted TCR gene and MHC class II-restricted TCR gene, respectively. Claims 15 and 16 specify further purifying the Th1 cells and Tc1 cells to which antigen specificity has been imparted by using antibody-bearing magnetic beads. Claim 17 specifies further comprising a step of mixing the separated Th1 cells and Tc1 cells in any given proportion.

Kessels teaches that "the antigen specificity of T lymphocytes is dictated solely by the T cell receptor (TCR) alpha and beta chains. Consequently, genetic transfer of TCR chains may be an appealing strategy with which to impose a desirable virus- or tumor-antigen specificity onto cytotoxic or helper T cell populations" (e.g. abstract). Kessels introduces F5 TCR chains into mouse spenocytes by retroviral infection and 5-15% of the total CD8+ T cells (cytotoxic T cells) expressed the F5 TCR. The F5 TCR-transduced T cells show a pronounced NP(366-374)-specific effector function and the retroviral introduction of TCRs leads to rapid generation of antigen-specific T cell immunity (e.g. p. 958, left column, 2nd paragraph). The CD8+ cells were purified from the total transduced splenocytes by using PE-anti-CD8 antibody (e.g. Figure 2). Kessels also introduces F5 TCR chains into total spleen cells, including CD4+ T cells (helper T cells) with pMX-F5 virus and 5-10% of the CD4+ T cells expressed the F5 receptor. However, "in contrast to the marked expansion of F5 TCR CD8+ T cells upon influenza A/NT/60/68 infection, no expansion of F5 TCR CD4+ T cells was detected…This lack of expansion of TCR-transduced CD4+ T cells was consistent with the idea that CD4 coreceptor binding and signaling is required for proper T cell activation; it suggests that, for the simultaneous induction of CD4+ T cell immunity, coapplication of retrovirus encoding MHC class II-restricted TCRs may be considered" (e.g. p. 959, left column, 2nd paragraph). The mouse is considered a patient. The splenocytes include lymphocytes and monocytes, which are leukocytes. The mouse splenocytes are leukocytes isolated from a patient.

Kessels does not specifically teach transducing Th1 cells or both Th1 and Tc1 cells with TCR gene and imparting antigen specificity to the Th1 cells or both Th1 and Tc1 cells. Kessels

also does not specifically teach separating the Th1 cells or Th1 and Tc1 cells with antibody-bearing magnetic beads or mixing separated Th1 cells and Tc1 cells in any proportion.

Fujio teaches that "transfer of the alphabeta TCR genes into T lymphocytes will provide a means to enhance Ag-specific immunity by increasing the frequency of tumor- or pathogen-specific T lymphocytes. Fujio co-transfect TG40 cells, a TCR-negative mouse T cell line, with retroviral vector expressing either of the class II MHC-restricted alpha or beta TCR gene specific for chicken OVA and results in expression of the clonotypic TCR in 44% of the CD4+ T cells (helper T cells). "The transduced cells showed a remarkable response to OVA323-339 peptide in the in vitro culture system ... Adoptive transfer of the TCR-transduced cells in mice induced the Ag-specific delayed-type hypersensitivity in response to OVA323-339 challenge" (e.g. abstract, p. 528, right column, last paragraph). The TG40 cells are considered induced helper T cells. The chicken OVA is considered a cancer-associated antigen.

Tsuji discloses preparation of nonspecific Tc1 cells, naïve CD8+ T cells from C57BL/6 mouse spleen and activation of those cells by 2ug/ml plate bound anti-CD3 mAb under Tc1, Tc2 or neutral condition (e.g. p. 389, right column). Antigen-nonspecific CD8+ T cells were polyclonally expanded in the presence of IL-2, Th1 cytokines (IFN-gamma and IL-12) and anti-IL-4 mAb. The polyclonally activated CD8+ cells were transduced by retrovirus expressing 2C TCR alpha or 2C TCR beta chain to generate antigen-specific cytotoxic T lymphcytes (CTL). The 2C-TCR gene-modified antigen specific Tc1 cells exhibit antitumor activity both in vitro and in vivo (e.g. abstract).

Nishimura teaches that it is difficult to maximize activation of antitumor immunity in vivo only by MHC class I-associated peptide, activation of class II-restricted helper T (Th) cells

is also required for induction of CTL which has recognized class I-associated tumor peptide (e.g. p. 363 (2-1 in the submitted copy filed 10-12-06).

It would have been prima facie obvious for one of ordinary skill in the art at the time of the invention to transduce Th1 cells with MHC class I or class II-restricted TCR gene, or to transduce both Th1 and Tc1 cells with either MHC class I or class II-restricted TCR gene because Kessels teaches retroviral transduction of mouse splenocytes, which includes both CD8+ T cells and CD4+ T cells, with MHC class I-restricted TCR (F5 TCR), Fujio teaches generation of MHC class II-restricted TCR transduced CD4+ T cells (helper T cells) that has antigen-specific immunity, Tsuji teaches transducing Tc1 cells with a retrovirus expressing 2C TCR gene, which is a MHC class I-restricted TCR, and the transduced Tc1 cells exhibit anti-tumor activity, and Nishimura shows that activation of class II-restricted helper T cells is required for induction of CTL (cytotoxic T cells) which recognized class I-restricted tumor peptide. The Th1 cells are CD4+ T cells and the Tc1 cells are CD8+ T cells, it would be obvious for one of ordinary skill in the art at the time of the invention to transduce both Th1 cells and Tc1 cells with TCR gene because the mouse splenocytes used by Kessels include both types of T cells and Fujio teaches transducing CD4+ T cells to obtain antigen-specific immunity. Although there is no expansion of CD4+ T cells taught by Kessels, however, Kessels points out that CD4+ T cells (helper T cells) may require expression of both MHC class I and class II-restricted TCR for the induction of CD4+ T cell immunity against tumor antigen. One of ordinary skill in the art would know how to transduce Th1 cells so as to impart antigen specificity to the Th1 cells. It should be noted that imparting antigen specificity to the Th1 cells and Tc1 cells only requires transducing the Th1 cells and Tc1 cells with a TCR gene that recognizes a cancer-associated antigen (see

claims 1 and 9). Whether the Th1 cells or Tc1 cells are induced or activated or not appears to be irrelevant in the instant invention.

One of ordinary skill would be motivated to transduce Th1 and Tc1 cells with either MHC class I or class II-restricted TCR gene in order to optimize the tumor antigen specificity of the Th1 cells or Tc1 cells. It would have been obvious for one of ordinary skill in the art to separate the Th1 cells or Th1 and Tc1 cells with antibody-bearing magnetic beads or mixing separated Th1 cells and Tc1 cells in any proportion because Kessels teaches purifying the CD8+ cells from the total transduced splenocytes by using PE-anti-CD8 antibody and it was known in the art to use antibody-bearing beads to separate cells with different antigen on the cell surface and determining various mixing proportion of Th1 cells and Tc1 cells would be routine optimization of a result effective variable. It would have been prima facie obvious to one of ordinary skill in the art to use TCR gene isolated from tumor specific human cytotoxic T cell clone because Fujio teaches using cDNA for TCR alpha and beta chains isolated from a cDNA library of DO11.10 TCR Tg splenocytes and since they are all TCR genes one would try to isolate the TCR genes from various sources so as to transduce Th1 or Tc1 cells with retroviral vector to provide a desirable virus- or tumor-antigen specificity onto the Th1 and Tc1 cells.

One having ordinary skill in the art at the time the invention was made would have been motivated to do so in order to generate 2C-TCR gene-modified antigen specific Tc1 cells for exhibiting antitumor activity as taught by Tsuji or to impose a desirable virus- or tumor-antigen specificity onto cytotoxic or helper T cell populations as taught by Kessels with reasonable expectation of success.

4. Claims 1, 5, 9 and 13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kessels et al., 2001 (Nature Immunology, Vol. 2, No. 10, p. 957-961) in view of Fujio et al., 2000 (Journal of Immunology, Vol. 165, p. 528-532), Tsuji et al., April 2003 (Cancer Science, Vol. 94, No. 4, p. 389-393), and Nishimura, T., 2000 (Cancer Treatment and Host, Vol. 12, No. 4, p. 363-373, IDS-CL) as applied to claims 1, 3, 4, 7-9, 11, 12, 15-17 and 22 above, and further in view of Gaiger et al., 2008 (US Patent No. 7323181 B2). Applicant's amendment filed 11-15-10 necessitates this new ground of rejection.

Claims 1 and 5 are directed to a process of preparing cells for cell therapy comprising inducing helper T1 cells that have a nonspecific antitumor activity from leukocytes isolated from a patient, and imparting antigen specificity to the helper T1 cells by transducing the helper T1 cells with a T cell receptor gene that recognizes a cancer-associated antigen. Claim 5 specifies the cancer-associated antigen is WT1. Claim 9 and 13 are directed to a process of preparing cells for cell therapy comprising inducing Th1 cells and Tc1 cells having a nonspecific antitumor activity and imparting antigen specifically to the Th1 cells and Tc1 cells by transducing the Th1 cells and Tc1 cells with a TCR gene that recognizes a cancer-associated antigen. Claim 13 specifies the cancer-associated antigen is WT1.

The teachings of Kessels, Fujio, Tsuji and Nishimura are as discussed above. Kessles, Fujio, Tsuji and Nishimura do not specifically teach using cancer-associated antigen Wilms' tumor 1 (WT1).

Gaiger teaches that "T cells specific for WT1 can kill cells that express WT1 protein. Introduction of genes encoding T-cell receptor (TCR) chains for WT1 are used as a means to quantitatively and qualitatively improve response to WT1 bearing leukemia and cancer cells"

(e.g. column 26, last paragraph). Non-specific T cells can be transfected with a polynucleotide encoding TCRs specific for a polypeptide described herein to render the host cell specific for the polypeptide. The hose cells can be used for adoptive immunotherapy of WT associated cancer (e.g. column 28, 1st paragraph).

It would have been prima facie obvious for one of ordinary skill in the art at the time of the invention to transduce Th1 cells or Th1 and Tc1 cells with a TCR gene for WT1 because Gaiger teaches transducing T cells with a gene encoding TCR chains for WT1 to render the host cell specific for adoptive immunotherapy of WT associated cancer.

One having ordinary skill in the art at the time the invention was made would have been motivated to do so in order to produce T cells expressing TCR specific for WT1 polypeptide for adoptive immunotherapy of WT associated cancer as taught by Gaiger with reasonable expectation of success.

Applicant argues that the TG40 cells described in Fujio result from the fusion of a cancer cell and a helper T cell and Fujio does not describe whether the transduced cells are Th1 cells or Th2 cells. Nishimura does not teach or suggest transduction of Th1 cells with TCR gene. The combination of Fujio and Nishimura would not teach or suggest to an ordinary artisan the induction of Th1 cells obtained from leukocytes isolated from a patient and the introduction of a MHC class I-restricted TCR gene into the Th1 cells. Expression of an exogenous TCR gene within the TG40 cells and introduction of class I-restricted TCR gene into Th1 cells isolated from a patient are completely different methods utilizing different cell mechanisms and functions

(amendment, p. 10-11). This is not found persuasive because of the reasons set forth above under 35 U.S.C. 103(a) rejeciton.

Kessels teaches retroviral transduction of mouse splenocytes, which includes both CD8+ T cells and CD4+ T cells, with MHC class I-restricted TCR (F5 TCR) and Fujio teaches generation of MHC class II-restricted TCR transduced CD4+ T cells (helper T cells) that has antigen-specific immunity, and Nishimura shows that activation of class II-restricted helper T cells is required for induction of CTL (cytotoxic T cells) which recognized class I-restricted tumor peptide. The Th1 cells are CD4+ T cells and the Tc1 cells are CD8+ T cells, in fact, the splenocytes include both Th1 cells and Tc1 cells. It would be obvious for one of ordinary skill in the art at the time of the invention to transduce both Th1 cells and Tc1 cells with TCR gene because the mouse splenocytes used by Kessels include both types of T cells and Fujio teaches transducing CD4+ T cells to obtain antigen-specific immunity. Although there is no expansion of CD4+ T cells taught by Kessels, however, Kessels points out that CD4+ T cells (helper T cells) may require expression of both MHC class I and class II-restricted TCR for the induction of CD4+ T cell immunity against tumor antigen. One of ordinary skill in the art would know how to transduce Th1 cells so as to impart antigen specificity to the Th1 cells. Although TG40 cells described by Fujio are not leukocytes isolated from a patient but Kessels teaches transducing mouse splenocytes with TCR gene and mouse splenocytes are leukocytes isolated from a patient. Further, Fujio teaches generation of MHC class II-restricted TCR transduced CD4+ T cells (helper T cells) that have antigen-specific immunity, and Th1 cells are CD4+ T cells. It would be obvious for one of ordinary skill in the art to transduce Th1 cells with TCR gene in view of the teachings of Kessels, Fujio, Tsuji and Nishimura. It also should be noted that

imparting antigen specificity to the Th1 cells and Tc1 cells only requires transducing the Th1 cells and Tc1 cells with a TCR gene that recognizes a cancer-associated antigen (see claims 1 and 9). Whether the Th1 cells or Tc1 cells are induced or activated or not appears to be irrelevant in the instant invention.

Applicant argues that Kessels fails to remedy the deficiencies of Fujio and Nishimura, in fact, Kessels teaches away from the claimed invention. Kessels shows that antigen specific helper T1 cells would not be induced. Tsuji fails to remedy the deficiencies of Fujio, Nishimura and Kessels because killer T cells have completely different properties and functions from helper T cells (amendment, p. 11-12). This is not found persuasive because of the reasons set forth above under 35 U.S.C. 103(a) rejection and the reasons set forth above.

Conclusion

No claim is allowed.

5. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37

CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (571) 272-0726. The examiner can normally be reached on Monday to Friday from 9:30 am to 6 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272-4517. The fax phone number for this group is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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